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Utility Estimates for Decision–Analytic Modeling in Chronic Heart Failure—Health States Based on New York Heart Association Classes and Number of Rehospitalizations

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ABSTRACT

Objectives: For economic evaluations of chronic heart failure (CHF) management strategies, utilities are not currently available for disease proxies commonly used in Markov models. Our objective was to estimate utilities for New York Heart Association (NYHA) classification and number of cardiovascular rehospitalizations.
Methods: EuroQol 5D data from the Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival Study trial were used to estimate utilities as a function of NYHA classification and number of cardiovascular rehospitalizations.
Results: In multivariate regression analyses adjusted for age (60 years), female sex and absence of further comorbidities, utilities for NYHA classes I–IV were 0.90, 0.83, 0.74, and 0.60 (P-value < 0.001 for trend). For cardiovascular rehospitalizations 0, 1, 2 and ≥3, the associated utilities were 0.88, 0.85, 0.84, and 0.82 (P-value < 0.001 for trend).
Conclusions: NYHA class and number of cardiovascular rehospitalizations are established proxies for CHF progression and can be linked to utilities when used as health states in a Markov model. NYHA class should be used when feasible.
Keywords: EQ-5D, heart failure, quality of life, quality-adjusted life-years, utilities.

Background

Because of the increasing incidence and costs associated with chronic heart failure (CHF) as well as health-care resource constraints, it is important to rationally evaluate new strategies in the management of CHF with respect to their effectiveness and cost-effectiveness [1]. In a recent systematic review, we identified 19 decision–analytic models evaluating new diagnostic and therapeutic strategies in CHF [2]. Although most models used thorough approaches, only six analyses reported clinical effectiveness outcomes in terms of quality-adjusted life-years. Moreover, utilities that can be linked to common proxy health states used in CHF decision–analytic cost–utility studies (e.g., using Markov models) to represent disease progression are not available in the literature.

To address the limitations of currently available data, we used primary data from the Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) to estimate utility values for patients with CHF according to New York Heart Association (NYHA) classification and number of cardiovascular (CV) rehospitalizations for use in future CHF decision models.

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Methods

The EPHESUS trial was a multicenter randomized controlled trial that investigated the effect of the aldosterone antagonist eplerenone in 6232 patients with CHF after acute myocardial infarction (AMI) [3]. End points of the study included all-cause mortality, CV mortality and CV hospitalization.

In a subsample of 1628 patients, health-related quality of life was assessed at months 0, 3, 6,12 and 18 using the EuroQol (EQ-5D) [4,5]; all data were used in the analyses except the baseline measurement that was excluded to mitigate the effect of the AMI on the EQ-5D score. The EQ-5D is a generic health status instrument that assesses five independent domains (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Recently, preference-based scoring algorithms have been developed to allow conversion of EQ-5D health states into population-specific utility weights. We used the utility value as a dependent variable in our analyses, weighting the EQ-5D score by the appropriate preference weight based on the subject's specific region of origin (United States—31%, Western Europe—52%, Latin America—14%) [6–8].

We performed univariate and multivariate linear regression analyses, employing a covariance modeling approach with an unstructured covariance matrix to account for repeated measurements and the high variability in utility estimates due to this inherent subjectivity [9]. The independent variables included NYHA classification or number of CV hospitalizations (0, 1, 2, ≥3) between study intake and the follow-up time point. Analyses were also adjusted for age, sex and cardiovascular comorbidities.

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Table 1 Results for the multivariate model based on NYHA class

	Estimate	Standard error	*P*-value
Intercept	0.785	0.037	<0.001
NYHA class 1	Reference group		
NYHA class 2	−0.071	0.006	*P*-value for trend <0.001
NYHA class 3	−0.161	0.009	
NYHA class 4	−0.302	0.026	
Age (per year)	0.002	0.001	0.014
$(\text{Age} - 50)^3+$	−2.22*E-06		
$(\text{Age} - 65)^3+$	4.44*E-06		
$(\text{Age} - 80)^3+$	−2.22*E-06		
Male	0.047	0.009	<0.001
History of diabetes	−0.024	0.009	0.007
History of ≥2 AMIs	−0.041	0.009	<0.001
History of stroke/TIA	−0.057	0.013	<0.001
History of PVD	−0.047	0.011	<0.001
History of COPD	−0.027	0.012	0.023
US/Canadian origin	Reference group		
European origin	−0.056	0.008	<0.001 (*F*-test)
Latin American origin	−0.005	0.012	

AMI, acute myocardial infarction; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; PVD, peripheral vessel disease; TIA, transitory ischemic attack; +, only include term if difference > 0.

Each model's goodness of fit was based on the Akaike information criterion (AIC) [10].

Results

We based our analyses on 4575 measurements from 1395 subjects with a mean age of 64 ± 12 years. Patient's characteristics in the subgroup (sub) were not significantly different from the full EPHESUS (full) dataset except as related to male sex (full, 74%; sub, 71%; *P*-value = 0.02), left ventricular ejection fraction (full, 33% ± 6; sub, 32% ± 7; *P*-value < 0.01), hypertension (full, 61%; sub, 55%; *P*-value < 0.01) and diabetes (full, 32%; sub, 26%; *P*-value < 0.01).

In univariate analyses, utilities associated with NYHA class I–IV were 0.855 (95% confidence interval [CI] 0.845–0.864), 0.771 (95% CI 0.761–0.781), 0.673 (95% CI 0.665–0.690) and 0.532 (95% CI 0.480–0.584), respectively (*P*-value for trend <0.001). For number of rehospitalizations (0, 1, 2, ≥3), the associated utilities in our univariate model were 0.812 (95% CI 0.802–0.821), 0.787 (95% CI 0.774–0.799), 0.769 (95% CI 0.751–0.787) and 0.746 (95% CI 0.727–0.765), respectively (*P*-value for trend <0.001).

Plotting the means of the observed versus predicted utilities stratified by deciles demonstrated an excellent fit for the models ($R^2 = 0.98$ for both models). Adjustment for age, sex and cardiovascular co-morbidities did not affect the trend in either analysis. Male sex was associated with significantly higher utilities in both analyses (0.04 for NYHA and 0.06 for rehospitalization).

Including age as a restricted cubic spline with knots at 50, 65 and 80 years improved the fit of both models significantly when compared with simple linear functions. Other covariates that had a significant effect on utilities in both models included history of an AMI before the entry of the study, history of a stroke or transient ischemic attack, history of peripheral vascular disease and history of chronic pulmonary obstructive disease. When the interaction between age and disease proxy was included, it did not affect the correlation between severity of disease and the decrement in utility in the NYHA class model, but it did affect the rehospitalization model with the lowest utility in the one rehospitalization group. Assessment of models that described the data best were based on AIC. Tables 1 and 2 provide the results from the final models that can be used to derive multivariate adjusted estimates. For example, in multivariate analyses adjusted for 60-year-old females without further co-morbidities, utilities for NYHA classes I–IV were 0.90, 0.83, 0.74 and 0.60, and 0.88, 0.85, 0.84 and 0.82 for cardiovascular rehospitalizations 0, 1, 2 and ≥3, respectively.

Discussion

Both proxies could be linked to utilities in a meaningful way and thus be used in future decision–analytic models. The goal of this analysis was not to develop a decision rule to predict an individual patient's utility as a function of these parameters over time, but rather to provide a set of empirically derived utility weights that can be easily linked to common disease proxies and that may be used to represent health states in future Markov models.

Both because of the subject matter of utility estimates and the design of the EPHESUS trial, we faced a number of analytic challenges. We first chose to employ a covariance modeling approach as opposed to treating each observation independently because this allowed us to utilize all available information while still accounting for the repeated measurements of each subject. This choice was particularly important because individual utilities are expected to have a high variability because they are influenced by various unmeasured patient characteristics as well as those covariates included in our model construct. In addition, because our sample was derived from a population of recent AMI patients, we chose to exclude the baseline utility assessment as well as the impact of time from our modeling strategy.

Although we found a significant interaction between our proxies of interest and age, but given the complexity associated with interpreting this interaction in the presence of age as a restricted cubic spline, we ultimately decided to exclude it from the model. Finally, despite its limitations, we felt that including the results from the rehospitalization model was useful, because number of rehospitalisations is a more objective end point than NYHA class and is therefore favored as an end point in many contemporary CHF trials. As a result, number of rehospitalizations is more likely to be available as a health state proxy for the disease modeler than NYHA class.

Table 2 Results for the multivariate model based on number of cardiovascular rehospitalizations

	Estimate	Standard error	*P*-value
Intercept	0.759	0.040	<0.001
0 rehospitalizations	Reference group		
1 rehospitalizations	−0.024	0.007	*P*-value for trend <0.001
2 rehospitalizations	−0.031	0.009	
≥3 rehospitalizations	−0.055	0.001	
Age (per year)	0.002	0.001	0.014
$(\text{Age} - 50)^3+$	−3.33*E-06		
$(\text{Age} - 65)^3+$	6.66*E-06		
$(\text{Age} - 80)^3+$	−3.33*E-06		
Male	0.054	0.009	<0.001
History of diabetes	−0.041	0.009	0.007
History of ≥2 AMIs	−0.061	0.009	<0.001
History of stroke/TIA	−0.074	0.014	<0.001
History of PVD	−0.046	0.012	<0.001
History of COPD	−0.035	0.013	0.023
US/Canadian origin	Reference group		
European origin	−0.060	0.009	<0.001 (*F*-test)
Latin American origin	0.014	0.013	

AMI, acute myocardial infarction; COPD, chronic obstructive pulmonary disease; PVD, peripheral vessel disease; TIA, transitory ischemic attack; +, only include term if difference > 0.

Conclusions

NYHA class and number of CV rehospitalizations are established proxies for CHF progression and can be linked to utilities when used as health states in a decision–analytic Markov model. If feasible, the NYHA class is preferable because its estimates are less sensitive to interaction with population age.

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